REMARKS

Remarks Regarding Supplemental Amendment

The present Supplemental Amendment is being filed at the request of Examiner Kishore. Although Amendment A was complete as filed by applicants, including Amendment A (20 pages), a Terminal Disclaimer (2 pages), a Declaration pursuant to 27 C.F.R. § 1.132 (6 pages), an Exhibit A (8 pages), and an Exhibit B (24 pages), applicants' representatives were informed by Examiner Kishore in a telephone interview that portions of Amendment A, including the Declaration, Exhibits A and B, and the Terminal Disclaimer were not received by him for review. As such, applicants are refiling as part of this Supplemental Amendment identical copies of the Remarks, Declaration, Exhibits A and B and the Terminal Disclaimer previously filed. Further, attached hereto is also a new **Exhibit C**, which is a copy of a return-receipt postcard filed along with the originally filed Amendment A listing each item mailed with Amendment A and having a USPTO acknowledgment stamp thereon confirming receipt of items listed. Applicants respectfully submit Exhibit C provides clear evidence that a complete copy of Amendment A, including attached supporting papers, was filed with and received by the Patent Office.

During the telephone interview, Examiner Kishore and Applicant's representative, James Daly, also discussed the currently pending claims as amended in Amendment A. Applicants and applicants' representatives wish to express their sincere appreciation to Examiner Kishore for giving applicants' representative an

opportunity to discuss the pending claims and to attempt to resolve all outstanding issues.

During the interview, changes to the claims were proposed and discussed, and amendments have now been made to the claims in accordance with those discussions. The changes are reflected in current amendments made to the claims in this Supplemental Amendment. Support for the claim amendments can be found in the specification as filed at paragraphs [0025]-[0027] (with reference to the Published U.S. Patent Application No. 2004/0137051 A1). Indication of changes are made with reference to the immediately preceding claims entered into the record, those being the claims set forth in Amendment A. Applicants respectfully submit the present amendments resolve all remaining issues and place the present application in proper condition for allowance. An early notice to such effect is earnestly solicited.

The remaining remarks set forth herein are identical to the remarks made in Amendment A and address rejections set forth in the first Official Action. Although previously submitted with Amendment A, they are repeated herein below to assure a complete record.

Serial No.: 10/627,195

Remarks Submitted with Originally Field Amendment A

I. Status Summary

Claims 1-27 were pending in the present application. Claims 1 and 7 have been amended and claims 4-6, 8-23, 26, and 27 have been cancelled without prejudice to the filing of one or more continuing patent applications directed to the subject matter of these claims. After entry of the present amendment, Claims 1-3, 7, 24, and 25 will remain pending in the present application. Applicants further request entry of new claims 28-33. No new matter has been added by the amendments.

Claims 1-27 have been rejected by the by the U.S. Patent and Trademark Office (hereinafter, "the Patent Office") under 35 U.S.C. § 103(a).

II. Response to 35 U.S.C. § 103(a) Claim Rejections

II.A. JP 03 236320 in view of Arakawa et al. and/or Puisieux et al.

Claims 1, 4, 5, 8, 9, 13-15, 18, 21, and 24-27 have been rejected by the Patent Office under 35 U.S.C. § 103(a) as being unpatentable over JP 03 236320 in view of the journal article to Arakawa et al. (*Tohoku J. Exp. Med.*, 1998, vol. 184, pp. 39-47; hereinafter, "Arakawa et al.") and/or the journal article to Puisieux et al. (*J. Drug Targeting*, 1994, vol. 2, pp. 443-448; hereinafter "Puisieux et al.").

The Patent Office argues JP 03 236320 teaches wound healing compositions comprising kojic acid and ATP, but admits that JP 03 236320 does not teach encapsulation of ATP in vesicles, as set forth in the rejected claims. The Patent

Office asserts Arakawa et al. and Puisieux et al. each teach liposomal compositions encapsulating ATP.

The Patent Office asserts it would have been obvious to one of skill in the art to combine the references. The Patent Office argues it would have been obvious to encapsulate ATP in liposomes because Arakawa et al. allegedly teaches liposomal encapsulation would result in sustained release of ATP and Puisieux et al. allegedly teaches liposomal encapsulation provides stability to ATP.

The positions of the Patent Office as summarized above with respect to the rejected claims are respectfully traversed as described below.

Initially, applicants note claims 4, 5, 8, 9, 13-15, 18, 21, 26, and 27 have been cancelled by the present amendment, thereby rendering the rejection of these claims effectively moot.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation in the references themselves to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claim 1 has been amended to more particularly recite the present subject matter. Claim 1 recites a wound-healing composition, comprising a wound-treating

component and fusogenic vesicles, wherein the vesicles comprise: a phospholipid which is a stable vesicle former, wherein the phospholipid is a phosphatidylcholine; at least one unstable vesicle forming member selected from the group consisting of another polar lipid, and PEG; and ATP at a concentration of 1 mM to 50 mM, wherein the vesicles have a ratio of the stable vesicle former to the unstable vesicle forming member of 1:1 to 500:1 and a fusion rate of at least 20 vesicle fusions/second. Support for the amendment to claim 1 can be found throughout the specification, including the claims as filed. Specifically, the addition of "fusogenic" finds support at paragraph [0018] of the present application (as published as US 2004/0137051). The incorporation of ATP as a component of the vesicle at a concentration of 1 mM to 50 mM finds support at paragraph [0038]. The inclusion of the stable vesicle former being a phosphatidylcholine can be found throughout the specification, including the Examples. The recitation of inclusion in the vesicle of an unstable vesicle forming member (i.e., members which are not stable vesicle formers) can be found in the specification at paragraphs [0029] – [0032]. The inclusion of a ratio of stable to unstable component can be found in the specification at paragraphs [0031] and [0032]. Therefore, applicants respectfully submit no new matter has been added by the amendment to claim 1.

Applicants respectfully submit that the cited references, either alone or in combination, do not teach every element of claim 1 or claims dependent therefrom, and further one of ordinary skill in the art would not be motivated to combine the teachings of JP 03 236320 with Arakawa et al. and/or Puisieux et al. As admitted by

the Patent Office, JP 03 236320 does not teach or suggest encapsulation of ATP into liposomes. Arakawa et al. and Puisieux et al. each teach the formation of stable liposomes to protect encapsulated ATP from hydrolysis and not unstable fusogenic vesicles, as recited in claim 1.

Arakawa et al. and Puisieux et al. describe stable vesicles of phosphatidylcholine to protect encapsulated ATP from hydrolysis. Arakawa et al. teaches a stable vesicle comprising a phosphatidylcholine and cholesterol. Arakawa et al. does not teach an unstable vesicle forming component in the liposome. Arakawa et al. appears to teach that the stable nature of the vesicles disclosed therein is a desirable trait in that the ATP is protected from hydrolysis and the vesicles will persist longer and provide slow release of ATP over time. See Arakawa et al. at p. 40, first paragraph. See also Arakawa et al. at p. 43, Table 3 and Figure 2, wherein the data acquired using the vesicles of Arakawa et al. indicates that only about 35% of the ATP was released 90 hours after administration. These data clearly indicate the liposomes taught by Arakawa et al. are very stable. Puisieux et al. also teaches formulation of stable liposomes for encapsulating and protecting ATP. Puisieux et al. teaches formulations of liposomes comprising phosphatidyl choline, cholesterol and in some embodiments sulfatides. Each of these components adds to the stability of the liposome and/or results in reduction of clearance by the reticulo-endothelial system. See Puisieux et al. at p. 445, second column. Puisieux et al. does not teach incorporating an unstable vesicle forming component into the liposomes. Both Arakawa et al. and Puisieux et al. describe stable vesicles that are

not fusogenic. Neither reference teaches a fusogenic vesicle comprising both a stable vesicle forming component and an unstable vesicle forming component, as presently set forth in claim 1.

Applicants respectfully submit that none of the cited references teach, either alone or in combination, a wound-healing composition comprising a fusogenic vesicle as set forth in claim 1. JP 03 236320 does not teach or suggest encapsulating ATP into liposomes at all. Arakawa et al. and Puisieux et al. only teach encapsulating ATP in stable vesicles, which have significantly distinct compositions and properties, as discussed above, than the fusogenic vesicles recited by claim 1. Further, one of ordinary skill in the art would not be motivated to incorporate the stable vesicles of Arakawa et al. and/or Puisieux et al. into a wound-healing composition of JP 03 236320 as the vesicles would not deliver ATP to tissues of the wound at significant levels to meet metabolic demands of the tissues and aid in wound-healing due, in part, to the stable nature of the vesicles.

Assuming *arguendo* the Patent Office has established a *prima facie* case of obviousness against claim 1 and claims dependent therefrom, applicants respectfully submit that claim 1 can be patentably distinguished over the combination of references in view of the unexpected results discovered by the applicants using formulations of the vesicles, as set forth in claim 1 and claims dependents therefrom. The present specification provides, particularly in Example 4, surprisingly effective delivery of ATP to tissues under a variety of physiological stresses, including wound healing, at levels sufficient for the stressed tissues to maintain metabolic functionality.

Further unexpected results for delivering ATP to cells in amounts sufficient to meet metabolic demand of the cells utilizing particular formulations of vesicles as recited in claim 1 are provided in the attached Declaration of Dr. William D. Ehringer submitted pursuant to 37 C.F.R. § 1.132 (hereinafter referred to as the "Declaration"). The surprisingly effective results utilizing the presently claimed vesicles, as disclosed in the present application and the Declaration, are unrecognized by any of the art of record. The present co-inventors have determined for the first time that amounts of ATP sufficient to meet metabolic demand of tissues of a wound can be delivered to cells through the incorporation of both a stable and an unstable vesicle forming component into a vesicle so as to provide a particular desired fusion rate of the vesicle with the cells of the wound tissue. Therefore, applicants respectfully submit claim 1 and claims dependent therefrom are patentably distinguished over the cited art, either alone or in combination.

In view of the above discussion, applicants respectfully request withdrawal of this rejection of claim 1. Further, as claims 24 and 25 depend either directly or indirectly from claim 1, applicants respectfully request withdrawal of the obviousness rejection of these claims as well. Applicants further respectfully request allowance of claims 1, 24, and 25 at this time.

II.B. JP 03 236320 in view of Arakawa et al. and/or Puisieux et al. further in view of Cullis et al.

Claims 4-10 and 13-18 have been rejected by the Patent Office under 35 U.S.C. § 103(a) as being unpatentable over JP 03 236320 in view of Arakawa et al. and/or Puisieux et al. further in view of U.S. Patent No. 6,417,326 to Cullis et al. (hereinafter, "Cullis et al.").

The Patent Office argues JP 03 236320, Arakawa et al., and Puisieux et al., together teach every element of the rejected claims, except the Patent Office admits the combination of references does not teach the use of PEG or fusion proteins in vesicles encapsulating ATP for wound healing, as set forth in the rejected claims. The Patent Office further argues and Cullis et al. teaches the use of PEG or fusion proteins in vesicles and it would be obvious to include the teachings of Cullis et al. because Cullis et al. allegedly teaches the advantages of fusogenic vesicles.

The positions of the Patent Office as summarized above with respect to the rejected claims are respectfully traversed as described below.

Applicants note claims 4-6, 8-10, and 13-18 have been cancelled and therefore the rejection of these claims is effectively rendered moot.

With regard to the rejection of claim 7, this claim is dependent from claim 1 and further recites that the at least one unstable vesicle forming member is PEG. As discussed in detail above, applicants respectfully submit the fusogenic vesicle composition recited in claim 1, and therefore also dependent claim 7, is patentably distinguished over JP 03 236320, Arakawa et al., and Puisieux et al. either alone or

in combination. Cullis et al. does not remedy the deficiencies of these references in that it also does not teach a wound-healing composition comprising a wound-treating component and fusogenic vesicles comprising ATP at a concentration of 1 mM to 50 mM, a phospholipid which is a stable vesicle former, wherein the phospholipid is a phosphatidylcholine, and at least one unstable vesicle forming member selected from the group consisting of another polar lipid and PEG, wherein the vesicle has a ratio of the stable vesicle former to the unstable vesicle forming member of 1:1 to 500:1 and a fusion rate of at least 20 vesicle fusions per second, and one of skill in the art would not be motivated to combine all of the references to render the rejected claims obvious in view of the references in combination.

Cullis et al. uses a lipid that does not form vesicles together with a bilayer stabilizing component (which is not a phosphatidylcholine as recited in claim 1 from which claim 7 depends). The bilayer stabilizing component will exchange out of the vesicles causing them to then fuse with target cells.

Cullis et al. uses a lipid adopting a non-lamellar phase, and therefore does not form stable vesicles. Added is a bilayer stabilizing component, which will stabilize vesicles formed from the lipid, which would otherwise adopt a non-lamellar phase. The vesicles thus formed are stable. Cullis et al. does not teach or suggest vesicles incorporating ATP within them. Upon administration, the bilayer stabilizing component exchanges out, causing the vesicle to become unstable and deliver the encapsulated drug. Examples of the bilayer stabilizing component include PEG conjugated to phosphatidylethanolamine (PEG-PE). See Cullis et al. at col. 14, lines

22-27. This component is distinct from the PEG recited in claim 7. First, it is chemically distinct in that the PEG recited in claim 7 is not conjugated to a lipid. Second, the chemical distinctions between the PEG-PE taught by Cullis et al. and the PEG recited in claim 7 provide functional differences. Unconjugated PEG as taught by the present specification and recited in claim 7 is an unstable vesicle forming member and therefore destabilizes a vesicle into which it is incorporated. In contrast, PEG-PE adds stability to a vesicle and therefore is a stable vesicle forming component, which Cullis et al. confirms by noting PEG-PE is a preferred stabilizing component. "In a presently preferred embodiment, the bilayer stabilizing component is polyethylene glycol conjugated to, i.e., coupled to, a phosphatidylethanolamine." Cullis et al. at col. 14, lines 24-27 (emphasis added). Cullis et al. does not appear to teach phosphatidylcholines as stable vesicle forming elements, as recited in claim 7.

Applicants respectfully submit that one of ordinary skill in the art would not be motivated to include the bilayer stabilizing component of Cullis et al. (e.g. PEG-PE) in a stable vesicle formed from a phosphatidylcholine (such as the vesicles of Arakawa et al. or Puisieux et al.), since these vesicles are already stable. Even so, the inclusion of PEG-PE (a stabilizing component) in a stable vesicle of Arakawa et al., or Puisieux et al. would only further stabilize the vesicle and would not provide an unstable fusogenic vesicle as recited in claim 7. Further, if the ATP of Arakawa et al. or Puisieux et al. were included in the vesicles of Cullis et al., then vesicles with the claimed compositions would not be formed. That is, no phosphatidylcholine as a stable vesicle forming component along with an unstable vesicle forming agent of

another polar lipid or PEG at a ratio of 1:1 to 500:1 to provide a fusion rate of at least 20 vesicle fusions per second, as recited in claim 1 from which claim 7 depends, would be produced by the combination of teachings with a reasonable expectation of success.

As none of the cited references, either alone or in combination, teach or suggest every element of claim 7, applicants respectfully request withdrawal of the rejection and allowance of claim 7 at this time.

II.C. JP 03 236320 in view of Arakawa et al and/or Puisieux et al. further in view of Cullis et al. and further in view of Ruckert

Claims 2, 11, 19, and 21-23 have been rejected by the Patent Office under 35 U.S.C. § 103(a) as being unpatentable over JP 03 236320 in view of Arakawa et al. and/or Puisieux et al., further in view of Cullis et al. and further in view of U.S. Patent No. 5,863,556 to Ruckert (hereinafter, "Ruckert").

The Patent Office argues JP 03 236320, Arakawa et al., Puisieux et al. and Cullis et al. together teach every element of the rejected claims, except the Patent Office admits the combination of references does not teach that a combination of anti-septic agents and anesthetic agents can be incorporated into a liposomal wound-healing composition. The Patent Office further argues it would have been obvious to one of skill in the art to include an additional wound-healing agent as Ruckert allegedly shows that a combination of wound-healing agents can be used.

The positions of the Patent Office as summarized above with respect to the rejected claims are respectfully traversed as described below.

Applicants note claims 11, 19, and 21-23 have been cancelled and therefore the rejection of these claims is effectively rendered moot.

With regard to the rejection of claim 2, this claim depends from claim 1 and additionally recites that the wound-treating component comprises at least one member selected from the group consisting of an antiseptic, an antibiotic, and an anesthetic. As discussed in detail above, applicants respectfully submit the fusogenic vesicle composition recited in claim 1, and therefore also dependent claim 2, is patentably distinguished over JP 03 236320, Arakawa et al., Puisieux et al., and Cullis et al., either alone or in combination. Ruckert does not remedy the deficiencies of these references in that it also does not teach a wound-healing composition comprising a wound-treating component and fusogenic vesicles comprising ATP at a concentration of 1 mM to 50 mM, a phospholipid which is a stable vesicle former, wherein the phospholipid is a phosphatidylcholine, and at least one unstable vesicle forming member selected from the group consisting of another polar lipid and PEG, wherein the vesicles have a ratio of the stable vesicle former to the unstable vesicle forming member of 1:1 to 500:1 and a fusion rate of at least 20 vesicle fusions per second. Ruckert appears only to teach stable vesicles comprised of lecithin and optionally also cholesterol. See Ruckert at col. 4, lines 46-51 and Example 1. Ruckert teaches that preferred liposome compositions permit protracted release over time of contents, which further indicates Ruckert teaches stable liposomes, which

differ significantly from the claimed fusogenic vesicles. See Ruckert at col. 5, lines 13-20 (reciting a preference for release rates of liposomes up to 30 hours duration).

As none of the cited references, either alone or in combination, teach or suggest every element of claim 2, applicants respectfully request withdrawal of the rejection and allowance of claim 2 at this time.

II.D. JP 03 236320 in view of Arakawa et al and/or Puisieux et al. further in view of Cullis et al. and further in view of Ruckert and further in view of Berthold

Claims 3, 12, and 20-23 have been rejected by the Patent Office under 35 U.S.C. § 103(a) as being unpatentable over JP 03 236320 in view of Arakawa et al. and/or Puisieux et al., further in view of Cullis et al., further in view of Ruckert and further in view of U.S. Patent No. 6,399,091 to Berthold (hereinafter, "Berthold").

The Patent Office argues JP 03 236320, Arakawa et al., Puisieux et al., Cullis et al. and Ruckert together teach every element of the rejected claims, except the Patent Office admits the combination of references does not teach the wound-treating component comprises becaplermin. The Patent Office further argues it would have been obvious to one of skill in the art to include becaplermin as Berthold teaches that this compound is a commonly used wound-healing agent.

The positions of the Patent Office as summarized above with respect to the rejected claims are respectfully traversed as described below.

Applicants note claims 12 and 20-23 have been cancelled and therefore the rejection of these claims is effectively rendered moot.

With regard to the rejection of claim 3, this claim depends from claim 1 and further recites that the wound-treating component comprises becaplermin. As discussed in detail above, applicants respectfully submit the fusogenic vesicle composition recited in claim 1, and therefore also dependent claim 3, is patentably distinguished over JP 03 236320, Arakawa et al., Puisieux et al., Cullis et al., and Ruckert either alone or in combination. Berthold does not remedy the deficiencies of these references in that it also does not teach a wound-healing composition comprising a wound-treating component and fusogenic vesicles comprising ATP at a concentration of 1 mM to 50 mM, a phospholipid which is a stable vesicle former, wherein the phospholipid is a phosphatidylcholine, and at least one unstable vesicle forming member selected from the group consisting of another polar lipid and PEG, wherein the vesicles have a ratio of the stable vesicle former to the unstable vesicle forming member of 1:1 to 500:1 and a fusion rate of at least 20 vesicle fusions per second. Berthold merely appears to suggest that becaplermin is a wound-healing agent.

III. Obviousness-Type Double Patenting Rejection

Claims 1-27 have been provisionally rejected based upon the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 and 35-46 of copending U.S. Patent Application No. 10/397,048 (referred to

herein as the "'048 Application"), from which the present application is a continuation thereof.

In an effort to address this rejection and expedite prosecution, applicants submit herewith a timely filed Terminal Disclaimer in compliance with 37 C.F.R. §1.321. Please charge the $65.00 small entity fee set forth in 37 C.F.R. §1.20(d) to Deposit Account No. 50-0426.

In submitting the attached Terminal Disclaimer, applicants do not acknowledge that the subject matter recited in claims 1-29 and 35-46 of the '048 Application and claims 1-27 of the present application are not patentably distinct. Moreover, applicants do not acknowledge that the subject matter described and claimed in the subject application is an obvious variation of the invention described and claimed in claims 1-29 and 35-46 of the '048 Application. Indeed, the Federal Circuit has noted that a Terminal Disclaimer "is not an admission of obviousness of the later filed claimed invention in light of the earlier filed disclosure for that is not the basis of the Disclaimer." Quad Environmental Technologies v. Union Sanitary District, 20 U.S.P.Q.2d 1392, 1394 (Fed. Cir. 1991).

The Federal Circuit further noted:

> In legal principle, the filing of a Terminal Disclaimer simply serves the statutory function of removing the rejection of double patenting and raises neither presumption nor estoppel on the merits of the rejection. It is improper to convert this simple expedient "obviation" into an admission or acquiescence or estoppel on the merit.
>
> *Quad Environmental Technologies*, 20 U.S.P.Q.2d at 1394-95.

Therefore, with the submission of the Terminal Disclaimer provided herewith, applicants are simply availing themselves of the statutory function of removing the double patenting rejection.

IV. New Claims

New claims 28-33 have been added by this amendment. Support for these claims can be found throughout the specification and claims as originally filed. Specifically, support for claim 28 can be found in claim 21 as originally filed. Support for claims 29 and 30 can be found at paragraph [0051]. Support for claims 31-33 can be found throughout the specification and particularly in Examples 1-4. Therefore, no new matter has been added by new claims 28-33

New claims 28-30 depend directly from claim 1. For the reasons set forth hereinabove, claims 28-30 are believed to be patentably distinguished over the cited art of record. Claims 31-33 recite a wound-healing composition comprising, in part, a vesicle comprised of ATP, DOPC, and POPA. Applicants respectfully submit none of the art of record teaches vesicles with the recited formulation. Allowance of claims 28-33 is therefore respectfully requested.

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CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON & TAYLOR, P.A.

Date: 10/25/05 By: _____

James Daly, IV
Registration No. 51,209

1577/2/2/2 AAT/JD/cab

Customer No: 25297

Enclosure: Copies of Executed Declaration of Dr. William Ehringer under 37 C.F.R. § 1.132 with Exhibits A and B
Copy of the Terminal Disclaimer
Exhibit C